

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
27 March 2003 (27.03.2003)

PCT

(10) International Publication Number  
**WO 03/024420 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 9/00**,  
9/16, 9/51, 31/55, 31/50, A61P 27/02
- (21) International Application Number: PCT/EP02/10314
- (22) International Filing Date:  
13 September 2002 (13.09.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
0122318.9 14 September 2001 (14.09.2001) GB
- (71) Applicant (for all designated States except AT, US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (for AT only): **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **AHLHEIM, Markus** [DE/DE]; Gewerbestrasse 9, 79219 Staufen (DE). **AUSBORN, Michael** [DE/DE]; Theodor-Heuss Strasse 96, 79539 Löffelach (DE). **BODMER, David** [CH/CH]; Rottrottenweg 8, CH-5313 Klingnau (CH). **SCHOCH,**
- Christian [CH/CH]; Lindenweg 15, CH-4132 Muttenz (CH).
- (74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).
- Published:  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OPHTHALMIC DEPOT FORMULATIONS FOR PERIOcular OR SUBCONJUNCTIVAL ADMINISTRATION

(57) Abstract: The present invention relates to ophthalmic depot formulations comprising an active agent, e.g. embedded in a pharmacologically acceptable biocompatible polymer or a lipid encapsulating agent, e.g. for periocular or subconjunctival administration.

WO 03/024420 A1

- 1 -

## OPHTHALMIC DEPOT FORMULATIONS FOR PERIOULAR OR SUBCONJUNCTIVAL ADMINISTRATION

The present invention relates to ophthalmic depot formulations for treatment of ocular diseases, in particular treatment of retinal and choroidal diseases.

- 5 Ocular diseases are difficult to treat as introduction of active agents into the eye and maintenance of therapeutically effective concentration thereof is difficult.

Oral administration of an active agent or parenteral administration of an active agent to a site other than the eye provides the active agent systemically. In order to achieve effective  
10 intraocular concentrations, systemic administration may necessitate administration of often unacceptably high levels of the active agent.

Injection of compositions comprising an active agent into the eye may be ineffective as the active agent may be washed out or is depleted from within the eye into the general  
15 circulation resulting in necessity for repeated administration, e.g. three injections in three to 42 days as described in US 5,632,984.

Introduction of slow release compositions, i.e. implants, into the eye, e.g. into an anterior segment or posterior segment of an eye as described in US 4,853,224, e.g. into the  
20 suprachoroidal space or pars plana of the eye as described in US 5,164,188, or e.g. into a site extrinsic to the vitreous comprising a suprachoroidal space, an avascular region of an eye, or a surgically-induced avascular region as described in US 5,824,072, by injection or surgical methods such as laser ablation, photocoagulation, cryotherapy, heat coagulation and the like is extremely painful and stressful for the patient. Implants may have to be  
25 removed when therapy is completed or no longer efficacious.

Applicants have found that ophthalmic depot formulations comprising an active agent may be administered, periocularly, e.g. retrobulbarly or sub-tenonally, or subconjunctivally.

Accordingly in one aspect, the present invention provides an ophthalmic depot formulation,  
30 comprising an active agent e.g. for periocular, e.g. retrobulbar or sub-tenon, or subconjunctival administration.

Ophthalmic depot formulations such as micro- or nanoparticle (hereinafter called microparticle), formulations, comprising an active agent e.g. embedded in a biocompatible pharmacologically acceptable polymer e.g. in an encapsulating polymeric matrix, or embedded in a lipid encapsulating agent have been found to be particularly suitable. The  
5 ophthalmic depot formulation may also comprise microparticles of essentially pure active agent, e.g. microparticles consisting of the active agent.

These microparticles have a high contact surface.

10 In one aspect, the present invention provides an ophthalmic depot formulation comprising microparticles of essentially pure active agent.

The microparticles of essentially pure active agent, e.g. microparticles consisting of the active agent, may be in amorphous or crystalline form e.g. with a particle size of 1 to 200  
15 microns.

In another aspect, the present invention provides an ophthalmic depot formulation such as microparticles comprising an active agent, e.g. embedded in a biocompatible pharmacologically acceptable polymer or a lipid encapsulating agent.

20 The depot formulations, e.g. in particular microparticle formulations, of the present invention are adapted to release all or substantially all the active material over an extended period of time, e.g. several weeks up to 6 months. The matrix, e.g. polymer or lipid matrix, if present, is adapted to degrade sufficiently to be transported from the site of administration within one  
25 to 6 months after release of all or substantially all the active agent.

The polymer matrix of polymeric microparticles may be a synthetic or natural polymer. The polymer may be either a biodegradable or non-biodegradable or a combination of biodegradable and non-biodegradable polymers, preferably biodegradable.

30

Suitable polymers include

- (a) linear or branched polyesters which are linear chains radiating from a polyol moiety, e.g. glucose,

- (b) polyesters such as D-, L- or racemic polylactic acid, polyglycolic acid, polyhydroxybutyric acid, polycaprolactone, polyalkylene oxalate, polyalkylene glycol esters of acids of the Kreb's cycle, e.g. citric acid cycle, and the like and combinations thereof,
- (c) polymers of organic ethers, anhydrides, amides, and orthoesters
- 5 (d) copolymers of organic esters, ethers, anhydrides, amides, and orthoesters by themselves or in combination with other monomers,
- (e) polyvinylalcohol.

10 The polymers may be cross-linked or non-cross-linked, usually not more than 5%, typically less than 1%.

The desired rate of degradation of polymers and the desired release profile for active agent may be varied depending on the kind of monomer, whether a homo- or a copolymer or whether a mixture of polymers is employed.

15

The preferred polymers of this invention are linear polyesters, and branched chain polyesters. The linear polyesters may be prepared from the  $\alpha$ -hydroxy carboxylic acids, e.g. lactic acid and glycolic acid, by the condensation of the lactone dimers, see e.g. US 3,773,919.

20

Linear polylactide-co-glycolides (PLG) which are preferably used conveniently have a molecular weight between 25,000 and 100,000 and a polydispersity  $M_w/M_n$  e.g. between 1.2 and 2.

25

The branched polyesters preferably used according to the invention may be prepared using polyhydroxy compounds e.g. polyol e.g. glucose or mannitol as the initiator. These esters of a polyol are known and described in GB 2,145,422 B. The polyol contains at least 3 hydroxy groups and has a molecular weight of up to 20,000, with at least 1, preferably at least 2, e.g. as a mean 3 of the hydroxy groups of the polyol being in the form of ester groups, which  
30 contain poly-lactide or co-poly-lactide chains. Typically 0.2% glucose is used to initiate polymerization. The branched polyesters (Glu-PLG) have a central glucose moiety having rays of linear polylactide chains, e.g. they have a star shaped structure. The preferred polyester chains in the linear and star polymer compounds preferably used according to the invention are copolymers of the alpha carboxylic acid moieties, lactic acid and glycolic acid,

or of the lactone dimers. The molar ratios of lactide: glycolide is from about 75:25 to 25:75, e.g. 60:40 to 40:60, with from 55:45 to 45:55, e.g. 55:45 to 50:50 the most preferred.

5 The branched polyesters having a central glucose moiety having rays of linear polylactide chains (Glu-PLG) may be prepared by reacting a polyol with a lactide and preferably also a glycolide at an elevated temperature in the presence of a catalyst, which makes a ring opening polymerization feasible.

10 The branched polyesters having a central glucose moiety having rays of linear polylactide chains (Glu-PLG) preferably have an average molecular weight  $M_n$  in the range of from about 10,000 to 200,000, preferably 25,000 to 100,000, especially 35,000 to 60,000 and a polydispersity e.g. of from 1.7 to 3.0, e.g. 2.0 to 2.5. The intrinsic viscosities of star polymers of  $M_n$  35,000 and  $M_n$  60,000 are 0.36 respectively 0.51 dl/g in chloroform. A star polymer having a  $M_n$  52,000 has a viscosity of 0.475 dl/g in chloroform.

15 Suitable lipid encapsulating agents for lipid microparticles include phosphatidyl compounds such as phosphatidyl choline (PC), phosphatidyl serine (PS), and phosphatidyl ethanolamine (PE), sphingolipids, cerebrosides, gangliosides, steroids, e.g. cholesterol, etc.

20 The terms microsphere, microcapsule and microparticle are considered to be interchangeable with respect to the invention, and denote the encapsulation of the active agent by the polymer, preferably with the active agent distributed throughout the polymer, which is then a matrix for the active agent. In that case preferably the terms microsphere or more generally microparticle are used.

25 The microparticles, e.g. microspheres or microcapsules, may have a diameter from a few submicrons to a few millimeters, e.g. from about 0.01 microns to about 2 mm, e.g. from about 0.1 microns to about 500 microns. For pharmaceutical micro-particles, diameters of at most about 250 microns, e.g. 10 to 200 microns, preferably 10 to 130 microns, more  
30 preferably 10 to 90 microns, even more preferably 10 to 60 microns, are strived for, e.g. in order to facilitate passage through an injection needle.

Typically, the active agent will be from about 1 to 80, more usually 10 to 75% by weight of the polymeric microparticles and from 1 to 20% by weight of the lipid microparticles.

In another aspect, the present invention provides a liquid formulation, comprising a pharmaceutical acceptable polymer and a dissolved or dispersed active agent. Upon injection, the polymer forms a depot at the injection site, e.g. by gelifying or precipitating.

5

The depot formulations, in particular microparticle formulations, according to the present invention are suitable for the incorporation of a large variety of water soluble or hydrophobic active agents.

10 Active agents of particular interest include

- i) anti-glaucoma drugs, such as the beta-blockers, e.g. timolol maleate, betaxolol, carteolol and metipranolol; epinephrine and prodrugs; such as dipivefrin; carbonic anhydrase inhibitors; such as dorzolamide, brinzolamide, acetazolamide, dichlorphenamide and methazolamide; dopaminergics, prostaglandins, docosanoids, alpha2 agonists; angiotensin II antagonists; alpha1 antagonists; cannabinoids; endothelin antagonists;
- 15 ii) miotics, e.g. pilocarpine, acetylcholine chloride, isofluorophate, demecarium bromide, echothiophate iodide, phospholine iodide, carbachol, and physostigmine;
- iii) drugs for treatment of macular degeneration, such as interferon, particularly  $\alpha$ -interferon; transforming growth factor (TGF), e.g. TGF- $\beta$ ;
- 20 iv) anti-cataract and anti-proliferative diabetic retinopathy (PDR) drugs, such as aldose reductase inhibitors: e.g. tolrestat, or angiotensin-converting enzyme inhibitors, e.g. lisinopril, enalapril;
- v) drugs for treatment of age-related exudative macular degeneration (AMD), e.g. ocular neovascular disease, such as staurosporines, phthalazine derivatives;
- 25 vi) anti-clotting agents, such as tissue plasminogen activator, urokinase, and streptokinase;
- vii) drugs for treatment of ocular inflammatory diseases such as cortico-steroids; e.g. prednisolone, triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, fluorometholone and the like, non-steroidal anti-inflammatory drugs, such as ketorolac tromethamine, diclofenac sodium, indomethacin, flurbiprofen sodium, and suprofen;
- 30 viii) antibiotics, such as loidine (cephaloridine), chloramphenicol, clindamycin, amikacin, gentamicin, tobramycin, methicillin, lincomycin, oxacillin, penicillin, amphotericin B, polymyxin B, cephalosporin family, ampicillin, bacitracin, carbenicillin, cephalothin,

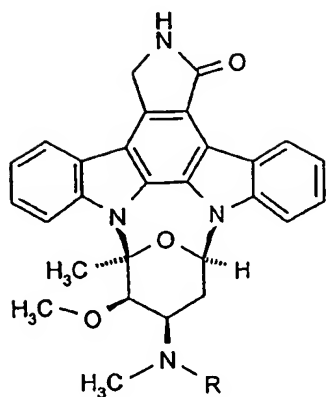
- 6 -

colistin, erythromycin, streptomycin, neomycin, sulfacetamide, vancomycin, silver nitrate, sulfoxazole diolamine, quinolones, and tetracycline;

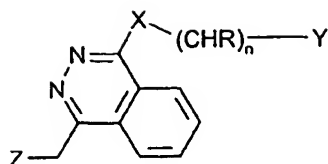
- ix) anti-fungal or anti-viral agents, such as miconazole, ketoconazole, idoxuridine, trifluridine, vidarabine (adenine arabinoside), acyclovir (acycloguanosine), gancyclovir, foscarnet sodium, cidofovir, valacyclovir, famciclovir, trisulfapyrimidine-2, nystatin, flucytosine, natamycin, aromatic diamidines e.g. dihydroxystilbamidine and piperazine derivatives, e.g. diethylcarbamide;
- x) cycloplegics and mydriatic agents, such as atropine, cyclopentolate, scopolamine, homatropine tropicamide and phenylephrine;
- xi) drugs for the treatment of ocular neurodegenerative diseases such as isopropyl unoprostone, glutamate receptor antagonists, e.g. memantine, caspase inhibitors, calcium antagonists, sodium channel blockers, NOS-2 inhibitors or neurotrophic factors, e.g. glial derived neurotrophic factor (GDNF) or ciliary neurotrophic factor (CNTF);
- xii) peptide drugs such as calcitonin, lypressin or a somatostatin or analogues thereof,
- xiii) anti-VEGF drugs;
- xiv) phosphodiesterase inhibitors;
- xv) antisense drugs such as fomivirsen sodium;
- xvi) immunosuppressive agents; such as azathioprine, cyclosporin A, methotrexate, colchicine;
- xvii) drugs for the treatment of ocular angiogenesis such as angiostatic steroids, PKC inhibitors, VEGF antagonists, COX2 inhibitors, ACE inhibitors or angiotensin II antagonists;
- xviii) free radical scavengers, e.g. alpha tocopherol, carotenoids, sulfhydryl-containing compounds.

Preferably, active agents are drugs for treatment of the orbit region and ocular appendages, and for treatment of retinal and choroidal diseases comprising but not limited to age-related macular degeneration, diabetic retinopathy, glaucoma, inflammation, e.g. endophthalmitis, and bacterial, fungal or viral infections. Even more preferably, the active agent is a staurosporine of formula (I), a phthalazine of formula (II) or an ophthalmically acceptable salt thereof. Even more preferred are the staurosporine of formula (I) wherein R is benzoyl (hereinafter compound A), and the phthalazine of formula (II) wherein Z is 4-pyrididyl, X is imino, n is 0, and Y is 4-chlorophenyl (hereinafter compound B).

- 7 -



(I)



(II)

wherein  
R is a hydrocarbyl radical R<sup>•</sup> or  
an acyl radical Ac

wherein  
n is 0 to 2,  
R is H or lower alkyl;  
X is imino, oxa, or thia;  
Y is aryl; and  
Z is unsubstituted or substituted pyridyl,  
or an N-oxide of the defined  
compound, wherein one or more N  
atoms carry an oxygen atom

In another aspect, the present invention provides depot formulations and microparticles comprising a staurosporine of formula (I), a phthalazine of formula (II) or an ophthalmically acceptable salt thereof e.g. embedded in a biocompatible pharmacologically acceptable polymer, e.g. for periocular, e.g. retrobulbar or sub-tenon, or subconjunctival administration.

The microparticles of this invention may be prepared by any conventional technique, e.g. solvent evaporation, organic phase separation, spray drying, solvent extraction at low temperature or emulsion method, e.g. triple emulsion method. Using the phase separation or emulsion technique, the polymer is precipitated together with the drug, followed by hardening of the resulting product.

In another aspect, the present invention provides for a process for the production of microparticles comprising the steps of

- a) dissolving the polymer or lipid encapsulating agent and the active agent in an organic solvent, e.g. methylene chloride,
- b) mixing the solution of a) with an aqueous solution of polyvinyl alcohol (e.g. 0.5%). e.g. using a static mixer

- c) collecting the generated microparticles, e.g. by a sedimentation, filtration or using a cyclon,
- d) optionally washing of microparticles e.g. in a buffered solution of e.g. pH 3.0 to 8.0 or distilled water, and
- 5 e) drying under vacuo e.g. at a temperature of 20°C to 40°C.

The invention also relates to the microparticles prepared by this process.

10 The microparticles and the depot formulations of the present invention are useful for treatment of the known ophthalmic indications of the particular active agent incorporated therein. The utility of the formulations of the present invention may be observed in standard animal trials and clinical trials.

15 In a further aspect, the present invention provides a method for treating an ocular disease which comprises:

- i) providing a depot formulation, e.g. a microparticle formulation, comprising an active agent e.g. embedded in a pharmacologically acceptable biocompatible polymer or a lipid encapsulating agent, and
- 20 ii) administering said depot formulation, e.g. microparticle formulation, periocularly, e.g. retrobulbarly or sub-tenonly, or subconjunctivally.

25 This method permits diffusion of said active agent from said depot formulation, e.g. a microparticle formulation, to the site of said ocular disease, e.g. the choroid, optic nerve, retina or vitreous. Preferably, the active agent is maintained at an effective dosage for said ocular disease at the site of said ocular disease for an extended period of time, e.g. for several weeks up to 6 months.

30 The depot formulations, e.g. microparticle formulations, may be administered, periocularly, e.g. retrobulbarly or sub-tenonly, or subconjunctivally in a variety of ways including injection, trocar etc. Preferably, the active agent particles or the microparticles are suspended in a suitable liquid carrier.

The exact amount of active agent embedded in the polymer, i.e. the exact amount of depot formulation, e.g. microparticles formulation, to be administered depends on a number of

factors, e.g. the condition to be treated, the desired duration of treatment, the rate of release of active agent and the degradability of the polymeric matrix. The amount of active agent required may be determined on the basis of known in vitro or in vivo techniques. Repeated administration of the depot formulation of the invention may be effected when the polymeric matrix has sufficiently degraded.

Large amounts of active agent, e.g. up to 300 mg of active agent, e.g. in form of a suspension, may be administered in a single administration, e.g. in one injection. Frequency of dosing is variably dependent upon the severity of the syndrome. For severe cases dosing may occur once a month. The frequency is reduced when signs of the disease state show improvement. At that time dosing may be as infrequent as one dose every four or five months.

Filling may be effected before or after sterilization of the depot formulation. Sterilization of the formulation of the present invention and the primary package can be effected, e.g. by gamma irradiation e.g. at an energy of 25kGy, without degradation of active agent and/or microparticles.

Following is a description by way of example only of depot formulations of this invention.

#### Example 1 to 3: Preparations of microparticles

	Ex. 1	Ex. 2	Ex. 3
compound A	0.10 g	0.25 g	0.50 g
Glu-PLG	0.90 g	0.75 g	0.50 g
methylene chloride	2.5 ml	4.0 ml	9.5 ml
1.5% aq. polyvinyl alcohol	500 ml	600 ml	900 ml
0.5% aq. polyvinyl alcohol	3 l	3 l	3 l

Compound A and the polymer Glu-PLG are dissolved in the methylene chloride. The resulting solution is pumped through a static mixer together with a 1.5% solution of polyvinyl alcohol in water into a stirred solution of polyvinylalcohol in water (0.5%). The resulting suspension is heated to 42-48°C with stirring within 60 min and kept at that temperature for further 30 min before the mixture is cooled down to about 22°C within 50 min. The suspension is allowed to sediment for approximately 10 min. The aqueous solution of

- 10 -

polyvinyl is reduced under vacuo. The microparticles are washed with water for approximately 5 min. After sedimentation for 10 min, the solution is removed and the microparticles are filtered through an Ultipor filter, washed with water and dried under vacuo.

Claims

1. An ophthalmic depot formulation comprising an active agent for periocular or subconjunctival administration.
- 5 2. A formulation according to claim 1 comprising of microparticles of essentially pure active agent.
3. A formulation according to claim 1 wherein the active agent is embedded in a biocompatible pharmacologically acceptable polymer or a lipid encapsulating agent.
- 10 4. A formulation according to claim 1 or 3 wherein the polymer is a polylactide-co-glycolide ester of a polyol.
5. A formulation according to any one of claims 1, 3 or 4 wherein the polymer is a 40/60 to  
15 60/40 polylactide-co-glycolide ester of a polyol.
6. A formulation according to any one of claims 1, and 3 to 5 comprising microparticles.
7. A formulation according to claim 6 wherein the external surface of the microparticles is  
20 substantially free of active agent.
8. A liquid formulation comprising a dissolved pharmaceutical acceptable polymer and a dissolved or dispersed active agent which formulation upon injection forms a depot at the injection site.
- 25 9. A formulation according to any preceding claim wherein the active agent is present in an amount of up to 300 mg per dose for single administration.
10. A formulation according to any preceding claim wherein the active agent is a staurosporine of formula (I), a phthalazine of formula (II) or an ophthalmically acceptable salt thereof.
- 30 11. A method for treating an ocular disease which comprises:
  - i) providing a depot formulation comprising an active agent, and

ii) introducing said depot formulation periocularly or subconjunctivally.

12. A method according to claim 11 wherein the active agent is embedded in a pharmacologically acceptable biocompatible polymer or a lipid encapsulating agent.

5

13. A method according to claim 11 or 12 wherein the active agent diffuses from said depot formulation to the site of said ocular disease.

10 14. A method according to any one of claims 11 to 13 wherein the active agent is maintained at an effective dosage for said ocular disease at the site of said ocular disease for an extended period of time.

15. A method according to any one of claims 11 to 14 wherein the active agent is maintained at an effective dosage for up to 3 months.

15

16. A microparticle comprising a staurosporine of formula (I), a phthalazine of formula (II) or an ophthalmically acceptable salt thereof embedded in a biocompatible pharmacologically acceptable polymer or a lipid encapsulating agent.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 02/10314

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K9/00 A61K9/16 A61K9/51 A61K31/55 A61K31/50 A61P27/02		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 322 319 A (WONG VERNON G) 28 June 1989 (1989-06-28) abstract page 2, line 50 -column 56 page 2, line 61 -page 3, line 9 page 3, line 21 - line 24 page 5, line 54 - line 56 claims 1-10	1-7,9, 11,12
X	US 5 632 984 A (WONG VERNON G ET AL) 27 May 1997 (1997-05-27) cited in the application abstract column 3, line 50 -column 5, line 60 claims 1-9	1-7,9, 11,12
-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in annex.		
<b>* Special categories of cited documents:</b> *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *Z* document member of the same patent family		
Date of the actual completion of the international search 27 January 2003		Date of mailing of the international search report 05/02/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Taylor, G.M.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 02/10314

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 773 919 A (BOSWELL G ET AL) 20 November 1973 (1973-11-20) cited in the application abstract column 1, line 60 -column 2, line 17 column 2, line 38 -column 3, line 6 column 9, line 55 - line 58 column 10, line 40 -column 11, line 49 examples 1-9 claims 1-16 ---	1-7,9
X	US 5 824 072 A (WONG VERNON G) 20 October 1998 (1998-10-20) cited in the application abstract column 2, line 20 - line 32 column 2, line 45 -column 3, line 51 column 8, line 38 -column 9, line 22 column 14, line 22 - line 45 claims 1-17 ---	1-3,6,7, 9-12,16
X	DE 37 22 837 A (RUETGERSWERKE AG) 19 January 1989 (1989-01-19) the whole document ---	1-3,6,7, 9,11,12
A	GB 2 145 422 A (SANDOZ LTD) 27 March 1985 (1985-03-27) cited in the application abstract page 1, line 5 - line 6 page 2, line 22 - line 32 examples 1-29 claims 1-29 ---	1-7, 9-12,16
A	WO 98 27962 A (ALZA CORP ;SHEN THEODORE T (US); BRODBECK KEVIN J (US)) 2 July 1998 (1998-07-02) abstract claims 1-27 ---	1-7, 9-12,16
P,A	WO 01 74389 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); BRAZZELL ROMULUS K) 11 October 2001 (2001-10-11) abstract page 3, compound CGP 79787D page 4, line 4 page 4, line 31 - line 32 claims 1-10 ---	1-7, 9-12,16
	---	

-/--

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 02/10314

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 28366 A (MIKSZTAL ANDREW R ;DURECT CORP (US); GIBSON JOHN W (US); CHAN TAI) 11 April 2002 (2002-04-11) abstract page 7, line 3 - line 4 page 17, line 23 - line 30 page 22, line 8 -page 23, line 5 page 26, line 11 - line 23 claims 22,23 -----	1-7, 9-12,16

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 8, 13-15

Present claims 8 and 13-15 relate to a formulation/method defined by reference to a desirable characteristic or property, namely

"which formulation upon injection forms a depot at the injection site" (claim 8);

"wherein the active agent diffuses from said depot formulation to the site of said ocular disease" (claim 13);

"wherein the active agent is maintained at an effective dosage for said ocular disease at the site of said ocular disease for an extended period of time" (claim 14);

"wherein the active agent is maintained at an effective dosage for up to 3 months" (claim 15).

The claims cover all formulations/methods having this characteristic or property, whereas the application provides support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT for only a very limited number of such formulations/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Art. 6 PCT). An attempt is made to define the formulations/methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for these claims.

In addition, claims 2 and 5 lack clarity within the meaning of Art. 6 PCT because the expression "essentially" has no well-accepted definition. This expression has been ignored for the purposes of the search.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/10314

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 8, 13-15  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International Application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/10314

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0322319	A	28-06-1989	US 4853224 A 01-08-1989
		AT 79252 T 15-08-1992	
		CA 1330421 A1 28-06-1994	
		DE 3873712 D1 17-09-1992	
		DE 3873712 T2 11-02-1993	
		EP 0322319 A2 28-06-1989	
		ES 2051882 T3 01-07-1994	
		JP 2975332 B2 10-11-1999	
		JP 10067650 A 10-03-1998	
		JP 11189527 A 13-07-1999	
		JP 2000702 A 05-01-1990	
		JP 8022814 B 06-03-1996	
		US 4997652 A 05-03-1991	
US 5632984	A	27-05-1997	WO 9503009 A1 02-02-1995
US 3773919	A	20-11-1973	CA 982479 A1 27-01-1976
		DE 2051580 A1 06-05-1971	
		FR 2070153 A5 10-09-1971	
		GB 1325209 A 01-08-1973	
		JP 50017525 B 21-06-1975	
US 5824072	A	20-10-1998	US 5443505 A 22-08-1995
		AU 1092495 A 06-06-1995	
		AU 731486 B2 29-03-2001	
		AU 8522998 A 26-11-1998	
		CA 2176145 A1 26-05-1995	
		CN 1139375 A 01-01-1997	
		EP 0729324 A1 04-09-1996	
		JP 9505300 T 27-05-1997	
		WO 9513765 A1 26-05-1995	
		US 5766242 A 16-06-1998	
DE 3722837	A	19-01-1989	DE 3722837 A1 19-01-1989
GB 2145422	A	27-03-1985	CH 656884 A5 31-07-1986
		AT 395584 B 25-01-1993	
		AT 271384 A 15-06-1992	
		AU 575066 B2 21-07-1988	
		AU 3234884 A 28-02-1985	
		BE 900406 A1 22-02-1985	
		CY 1556 A 22-03-1991	
		DE 3430852 A1 14-03-1985	
		DK 407284 A 27-02-1985	
		ES 8706750 A1 16-09-1987	
		FR 2551072 A1 01-03-1985	
		GR 80184 A1 02-01-1985	
		HK 67390 A 07-09-1990	
		HU 38265 A2 28-05-1986	
		IE 58818 B1 17-11-1993	
		IL 72763 A 29-02-1988	
		IT 1176629 B 18-08-1987	
		JP 2109364 C 21-11-1996	
		JP 8019226 B 28-02-1996	
		JP 60076531 A 01-05-1985	
		LU 85514 A1 24-04-1985	
		NL 8402547 A ,B, 18-03-1985	
		NZ 209335 A 30-08-1988	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/10314

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2145422	A		PH 23556 A	25-08-1989
			PT 79129 A ,B	01-09-1984
			SE 462098 B	07-05-1990
			SE 8404225 A	27-02-1985
			SG 53590 G	26-10-1990
			US 5922338 A	13-07-1999
			US 5922682 A	13-07-1999
			ZA 8406634 A	30-04-1986
WO 9827962	A	02-07-1998	AT 203157 T	15-08-2001
			AU 5609798 A	17-07-1998
			AU 739469 B2	11-10-2001
			AU 5615498 A	17-07-1998
			DE 69705746 D1	23-08-2001
			DE 69705746 T2	31-10-2001
			DK 949905 T3	22-10-2001
			EP 0949905 A2	20-10-1999
			EP 0959873 A2	01-12-1999
			ES 2158611 T3	01-09-2001
			GR 3036599 T3	31-12-2001
			HK 1020009 A1	02-11-2001
			JP 2002512597 T	23-04-2002
			JP 2001509146 T	10-07-2001
			NZ 335851 A	23-02-2001
			PT 949905 T	28-12-2001
			WO 9827962 A2	02-07-1998
			WO 9827963 A2	02-07-1998
			US 6468961 B1	22-10-2002
			US 2002034532 A1	21-03-2002
			US 6331311 B1	18-12-2001
			US 6130200 A	10-10-2000
WO 0174389	A	11-10-2001	AU 5040101 A	15-10-2001
			BR 0109499 A	10-12-2002
			WO 0174389 A2	11-10-2001
			EP 1265636 A2	18-12-2002
			NO 20024486 A	19-09-2002
			US 2001039438 A1	08-11-2001
WO 0228366	A	11-04-2002	AU 9677001 A	15-04-2002
			WO 0228366 A2	11-04-2002